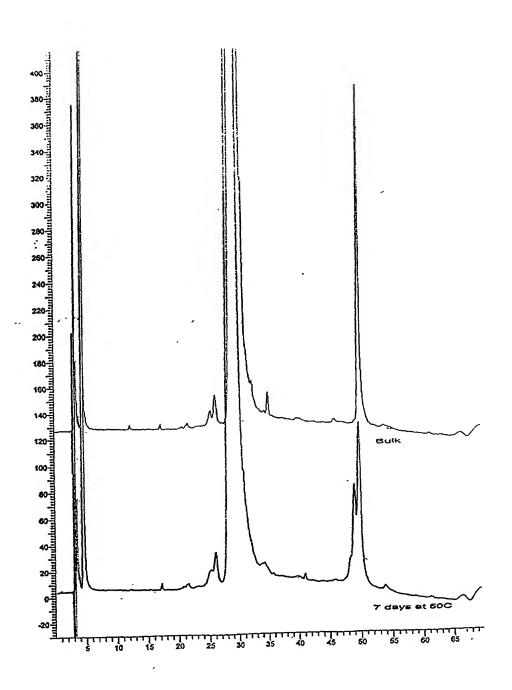
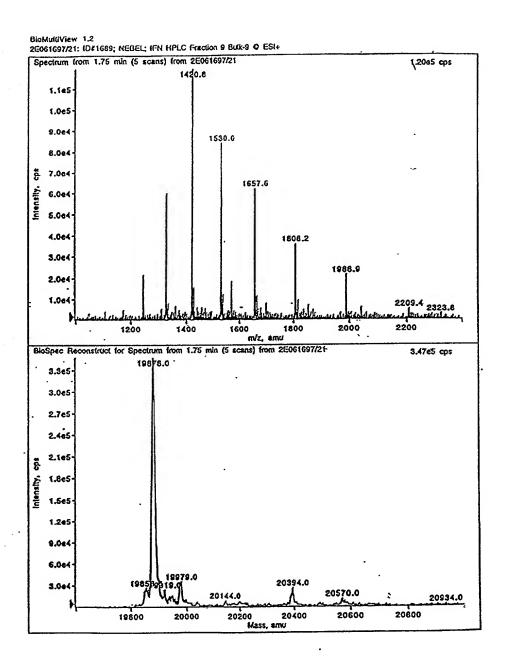
Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)



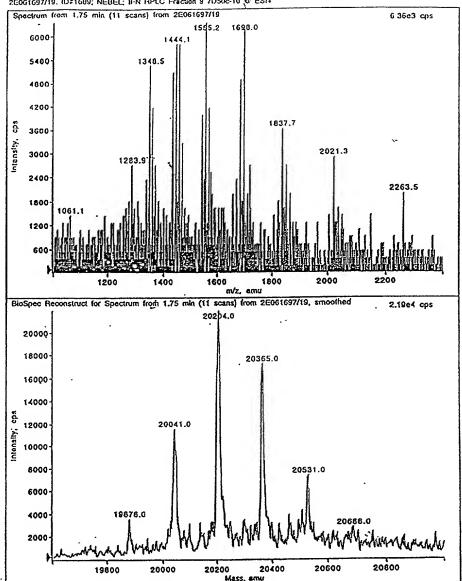
Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)



Inventor(s): Wolfe et al

Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)

| BIOMUNITY | 1 2 | 2E0G1697/19. ID#1689; NEBEL; NEW HPLC Fraction 9 7050c-10 @ ESI+



Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)

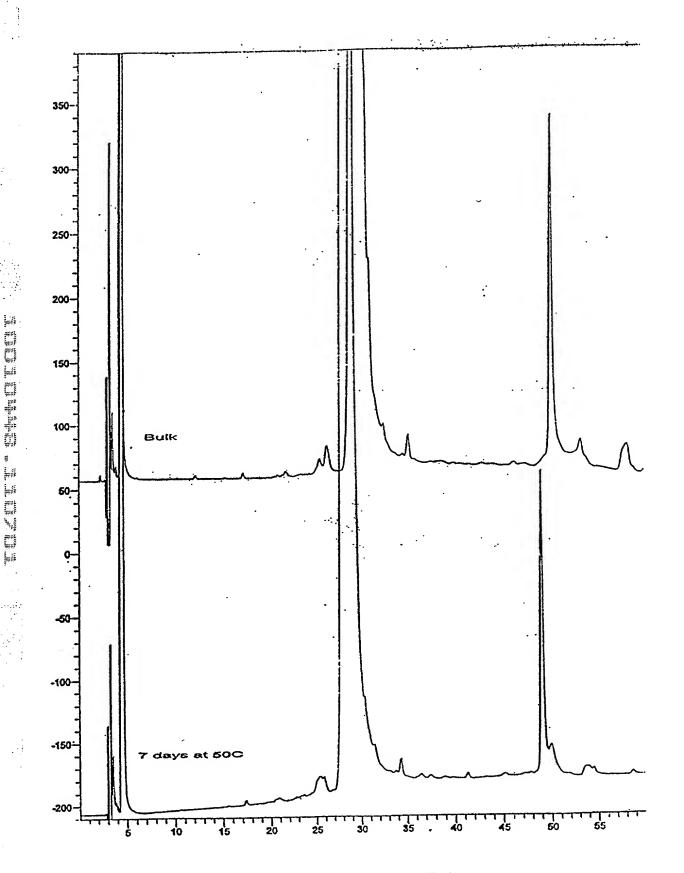
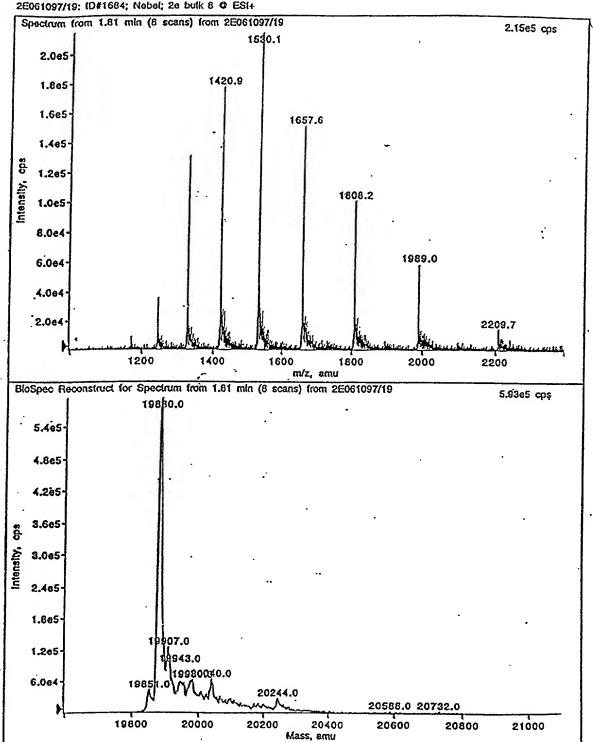


FIGURE 4

Inventor(s): Wolfe et al Application No: Not Assigned

Atty Dkt No: PP16166.003(35784/240745)

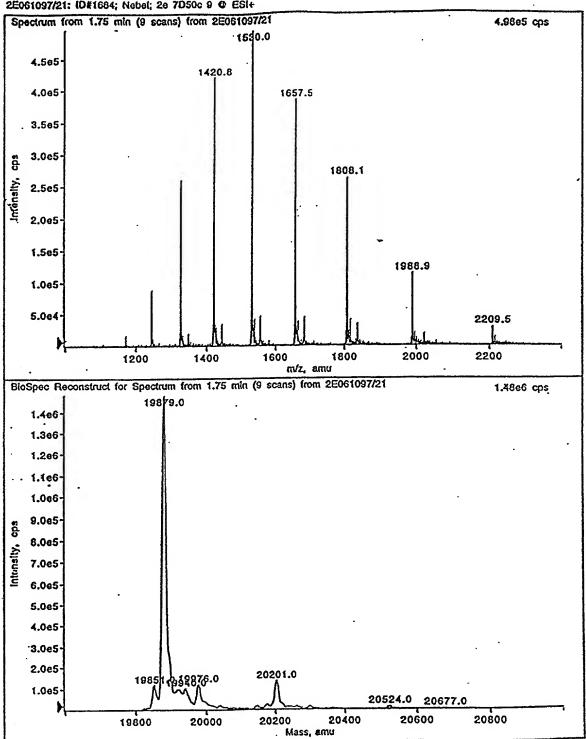
BioMultiView 1.2 2E061097/19: ID#1684; Nebel; 2e bulk 8 © ESI+



Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al Application No: Not Assigned

Atty Dkt No: PP16166.003(35784/240745)

- BloMuttiView 1.2 2E061097/21: ID#1684; Nebel; 2e 7D50c 9 © ESI+



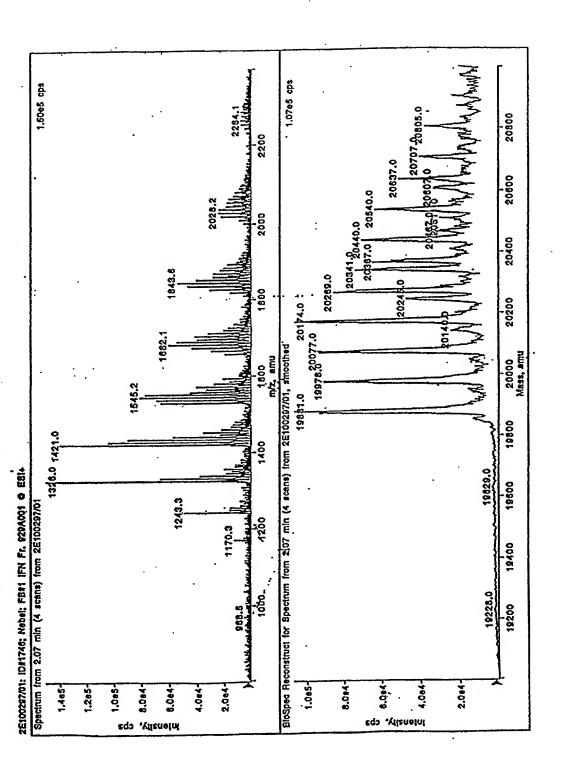


FIGURE 7

BIOMUIIVIOW 1.2 2E100297/04: 10#1746; Nobel; FB#4 IFN-1 929A004.73W 'O ESI+

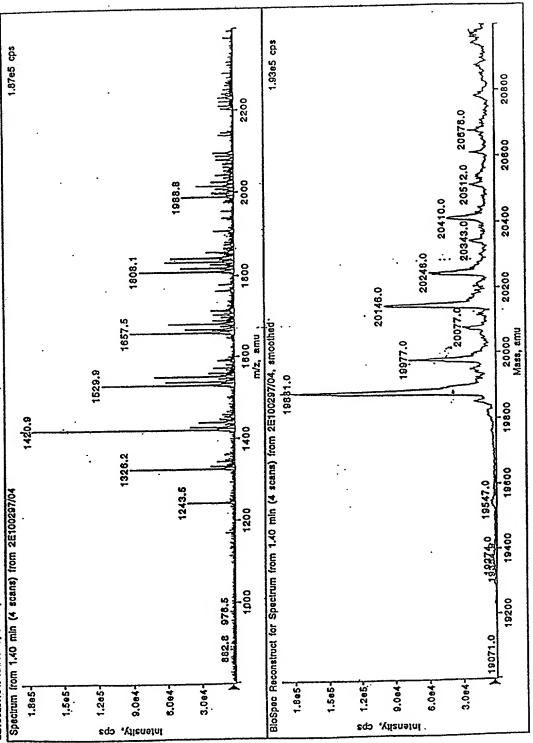


FIGURE 8

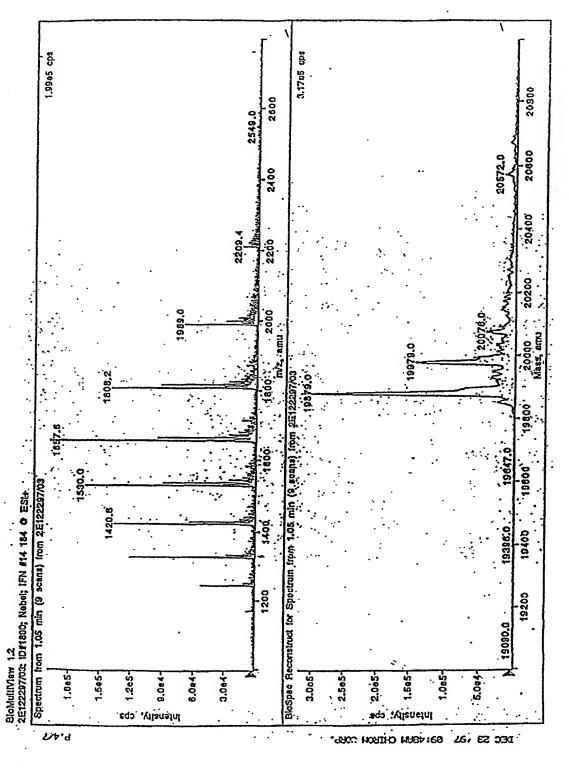


FIGURE 9

Inventor(s): Wolfe et al
Application No: Not Assigned

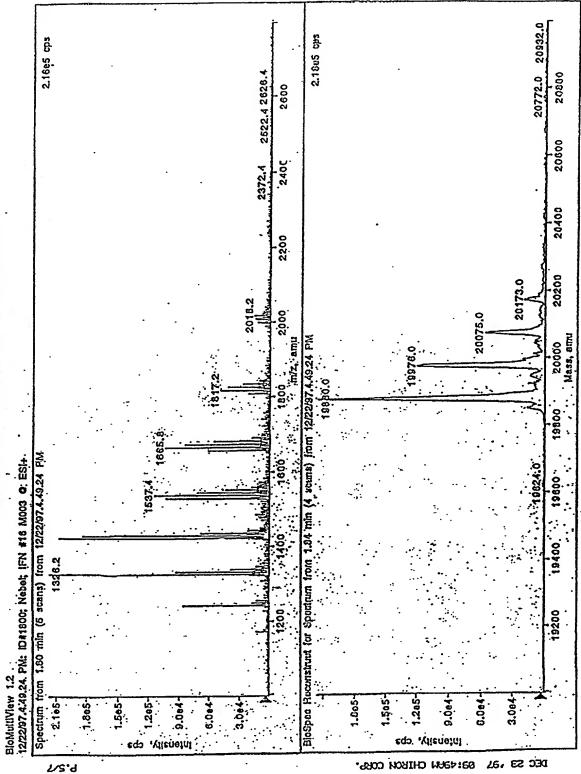


FIGURE 10

Intle: Stabilized Interferon Compositions Inventor(s): Wolfe et al Application No: Not Assigned Application No: Philosophy (3.78/20145)

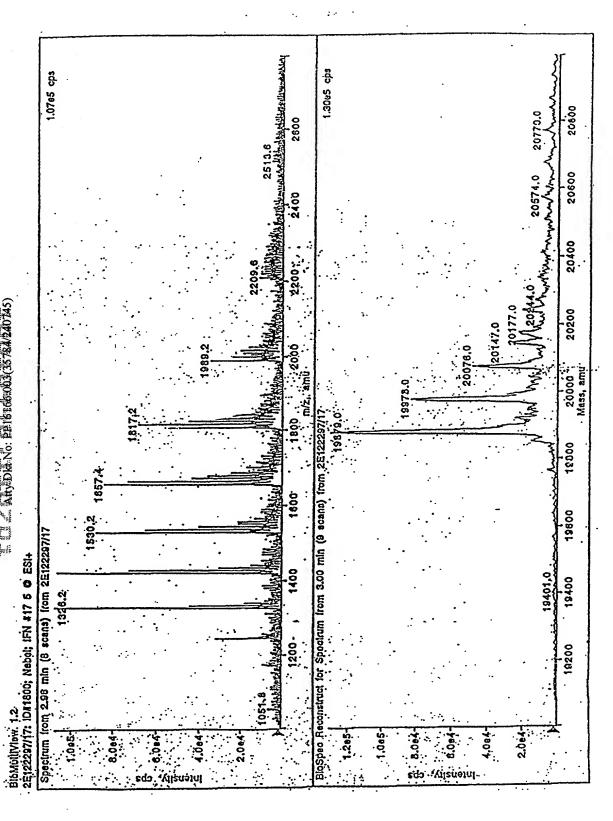


FIGURE 1

Inventor(s): Wolfe et al Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)

### STABILITY EVALUATION DATA

Interferon- $\beta$ -1b: Dextrose Formulation

Product	Storage	Months	Potency	Chapardeted	m . 1 mm ro
Troduct	Temperature	Ivioliuis	(Specific	Glucosylated	Total IFNβ-1b
	(upright,		activity,	IFN-β-1b	concentration
	protected from		IU/mg)	concentration	(mg/ml)
	light)		10/mg)	(mg/ml)	
IFN-β 1b	+ 8°C	0	$2.13 \times 10^{7}$	<0.02	0.22
0.25 mg/mi	+ 8°C	1	$2.50 \times 10^{7}$	<0.02	0.23
1.25 % dextrose	+ 8°C	2	$2.71 \times 10^{7}$	<0.02	0.23
1.25 % HSA	+ 50°C	2.2	$3.52 \times 10^{7}$	<0.02	0.23
Lot:	+ 50°C	2.5	$4.68 \times 10^{7}$	Too degraded	Too degraded
MBAPM023	+ 50°C	2.7	$4.60 \times 10^{7}$	Too degraded	Too degraded
7200-607	+50°C	3	$5.61 \times 10^{7}$	Too degraded	Too degraded
	+8°C	3	$2.41 \times 10^{7}$	<0.02	0.23
IFN-β 1b	+25°C	0	$2.12 \times 10^{7}$	<0.02	0.22
0.25 mg/ml	+ 25°C	1	$2.05 \times 10^{7}$	<0.02	0.21
1.25 % dextrose	+25°C	2	$3.24 \times 10^{7}$	<0.02	0.22
1.25 % HSA	+ 50°C	2.2	$3.88 \times 10^{7}$	<0.02	0.21
Lot:	+ 50°C	2.5	$4.64 \times 10^{7}$	Too degraded	Too degraded
MBAPM027	+ 50°C	2.7	$5.08 \times 10^{7}$	Too degraded	Too degraded
7200-600	+ 50°C	3	$5.91 \times 10^7$	Too degraded	Too degraded
	+25°C	3	$2.51 \times 10^{7}$	<0.02	0.23
IFN-β 1b	+37°C	0	$2.12 \times 10^{7}$	<0.02	0.22
0.25 mg/ml	+37°C	1	$2.85 \times 10^{7}$	<0.02	0.18
1.25 % dextrose	+37°C	2	$3.88 \times 10^{7}$	<0.02	0.23
1.25 % HSA	+ 50°C	2.2	$4.28 \times 10^{7}$	Too degraded	Too degraded
Lot:	+50°C	2.5	$4.88 \times 10^{7}$	Too degraded	Too degraded
MBAPM027	+ 50°C	2.7	$4.72 \times 10^7$	Too degraded	Too degraded
7200-600	+ 50°C	3	$5.44 \times 10^7$	Too degraded	Too degraded
	+37°C	3	$4.08 \times 10^{7}$	Too degraded	Too degraded

Inventor(s): Wolfe et al

Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)

### STABILITY EVALUATION DATA

### Interferon- $\beta$ -1b: Highly Purified Mannitol Formulation

Product	Storage	Months	Potency	Glucosylated	Total IFNβ-1b
110000	Temperature	1,1011410	(Specific	IFN-β-1b	concentration
	(upright,		activity,	concentration	(mg/ml)
	protected from		IU/mg)	(mg/ml)	
	light)			, ,	
IFN-β 1b	+8°C	0	$1.40 \times 10^{7}$	<0.02	0.22
0.25 mg/ml	+ 8°C	1	$1.52 \times 10^7$	<0.02	0.21
1.25 % highly	+8°C	2	$1.69 \times 10^{7}$	<0.02	0.22
purified	+50°C	2.2	$1.68 \times 10^{7}$	<0.02	0.22
mannitol	+ 50°C	2.5	$1.68 \times 10^{7}$	<0.02	0.21
1.25 % HSA	+ 50°C	2.7	$1.54 \times 10^{7}$	· <0.02	0.21
	+50°C	3	$1.53 \times 10^{7}$	<0.02	0.22
	+8°C	3	$1.62 \times 10^{7}$	<0.02	0.23
IFN-β 1b	+25°C	0	$1.40 \times 10^{7}$	<0.02	0.22
0.25 mg/ml	+25°C	1	$1.58 \times 10^{7}$	<0.02	0.21
1.25 % highly	+ 25°C	2	$1.88 \times 10^{7}$	<0.02	0.22
purified	+ 50°C	2.2	$1.84 \times 10^{7}$	<0.02	0.22
mannitol	+ 50°C	2.5	$1.67 \times 10^{7}$	<0.02	0.20
1.25 % HSA	+ 50°C	2.7	$1.61 \times 10^{7}$	<0.02	0.21
	+ 50°C	3	$1.53 \times 10^{7}$	<0.02	0.22
	+ 25°C	3	$1.59 \times 10^{7}$	<0.02	0.23
IFN-β 1b	+37°C	0	$1.40 \times 10^{7}$	<0.02	0.22
0.25 mg/ml	+ 37°C	1	$1.50\times10^7$	<0.02	0.21
1.25 % highly	+37°C	2	$1.80 \times 10^{7}$	<0.02	0.21
purified	+ 50°C	2.2	$1.86 \times 10^{7}$	<0.02	0.21
mannitol	+ 50°C	. 2.5	$1.84 \times 10^{7}$	<0.02	. 0.20
1.25 % HSA	+ 50°C	2.7	$1.73 \times 10^{7}$	<0.02	0.20
	+ 50°C	3	$1.41 \times 10^{7}$	<0.02	0.20
	+37°C	3	$1.53 \times 10^{7}$	<0.02	0.22

Title: Stabilized Interferon Compositions
Inventor(s): Wolfe et al

Application No: Not Assigned —
Atty Dkr No PP fol 66:003 (35784/240745)

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT RESULTS FOR LOT MEDPHIDS (MANNITOL FORMULATION)

Sterllity		Pass		:	:	1	:	ı	ı	ı	ı	Pass		í	1	1	ı	ı	1	I	:	2	Pass	Pass	
Confaincr Closure Integrity Dye Leak Test		1		<b>i</b> i	<b>)</b>	* *	ï	:	2	ı	1,	Pass		ŧ	:	i	:	1	:		l.	•	Pass	Pass	
Polency CPE Blowny	(TUME x 10')	23	ı	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	}	i	i 2	t =	3 .	7:	2 :	Ž	1	;	ì	1	:	31	31.	4		1	E E	22 to 45 x 107	
pH Upon Reconstitution		7.4	:	£		}	۲ ۾	, t-		7 %	t 4	3	1	7.7	3	ı	:	7.4	7.5	7.5	7.		4.4	27-17	
Residual	(9% by weight)	0.3	70	0.5	70	<b>;</b> (	2	50	Š	2 6	3 5	25	7.0	; ÷	3 8	P .	I ¦	2.0	0.8	80	1.0	;	177	NETT3%	
Upon Recon. Color		ŧ	ŧ	•	1	ı	. 1	ŧ	:	coloriess	>HV.	( and	1	48γ.	į	ı	1	BY	æx.	ı	colorless	700	1071	Colorless to	MATTER
Upon Recon. Clarity		:	1		1	;	ı	1	:	п	₹	i	ŧ	₽	۱ ,	1 1	;	₹	₹	1	₩	Ę	<b>j</b>	NMT Refill	
Upon Upon Reconstitution C		clear, slightly yellow	ı	clear, colorless	ŧ	:	clear, colorless	clear, colorless	clear, colorless	clear, slightly rellow	clear, slightly vellow		1	clear, coloriess		1	of see all alone and the see	ciem, augusty years	clear, colorless	clear, colorless	ciest, slightly yellow	clear effoltive wellman	many from the second	Clear, colorless to light yellow	•
Plug (cake)		white	ı	white	ł	;	white	white	white	white	white		ı	while	i	1	safting	200	white	white	white	white		White	
Months in Starage		0	7	m	4	'n	9	σ.	업	13	*		и	m	4	<b>'</b>	. 12	<b>.</b>	<b>5</b> . 1	ដ	£	74		European Specifications:	
Storage Temp.	9		4	~	*	*	4	*	4	4	4		8	æ	33	8	Ę	3 (	<b>R</b>	윩	윤	33		Etropean Sj	

## FIGURE 14(A)

Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al Inventor(s): Wolfe et al Application: No No: No LASS gred La Atty Dkt No: PP16166.003(35784/240745)

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT RESULTS FOR LOT MBDPN006 (MANNITOL FORMULATION)

(mg/m))	(mZm)
	1
	1
	1
	:
	<b>40.05</b>
0.25***	<0.02
0.23***	<0.02***
	<0.02
	40.02
	40.02
	1
	<b>20.02</b>
0.25***	40.02
0.23***	<0.02***
	40.02
	<b>&lt;0.02</b>
	~0.02
2	MATOR
	30 2 — — — — — — — — — — — — — — — — — —

# FIGURE 14(B)

Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al.

Tritle: Application with Assigned Tritle Atty Dkt No: PP16166.003(35784/240745)

STABILITY OF BETASERON J BETAFERON FIXAL CONTAINER PRODUCT RESULTS FOR LOT MEDPINGUS (MAINITOL FORMULATION)

Steedilly		Pass		ŧ	:	:	1	:	:	:	•	r Pass		ı	i	ı		ı	f	ı	ı	ł	Pass		Part
Container Closure Integrity Dye Leak Test		i		1	:	:	•	;	i	1	1	Pess			1	ı	:	! <b>:</b>	l	:	1	:	Pass		Pass
Fotency CFE Blonsmy	(TUME × 107)	2.9			;	Į.	1 ;	33	34	32	2.8	33		ŧ	3,0	:	2	3.4	76	<b>t</b>	7.	29	32		221045×107
pH Upon Reconstitution		7.3	1	7.4	<b>:</b> 1	:	: }	2	7.6	7.6	7.5	<b>3</b> 2		4 }	22	1	1	7.5	3.6	36	9 1	7.5	7.6		7.1-7.5
Residual . Malsture	(% by weight)	ຄ	50	50	¥	}	1 2	3 ;	9.0	9,0	98	970	8	3 6	 0	9.0	1	0.7	01	0	3 :	2	11		NAIT 3%
Upon Recon. Color		1	ı		i		}	ı	ı	ı	colorless	>BY,	;	•	:	ŧ	•	BY	&¥.		an landar	Colonics	>BY,		Colorless to alightly yellow BY <sub>5</sub>
Upon Recon. Clarity		1	1		1	:	: 1	1	:	ŧ -	₹	₹	1	Ę	7	1	1	.₩	ㅁ	. \$	E	<b>1</b> !	₹		MATRETH
Upon Reconstitution		ciçar, coloriess		clear, colorless	:		clear coloriese	ماست مداره	elem erlados	cicit, colonicis	clent, colodes	clear, alightly yellow		cirar colodes		ł	ı	clear, slightly yellow	clear, colociess	clear,colorless	ciercoloriese	10 10 10 10 10 10 10 10 10 10 10 10 10 1	בוכבר בווצחוה אבווסא		Clear, coloriess to light yellow
Cake)		white	1	white	ı	1	white	white	al Aller	AUTO.	White	white	ı	white		1 :	1 ;	*Hit	white	white	white	1	A mile		Work
Months in Storage		0	ч	٣	4	47	9	o	2 /	3 :	۶ŗ.	*	7	t th	٧	· v	,	•	Φ	ដ	*2	5	\$		Europein apoenications:
Storage Temp.			4	<b>→</b>	<b>~</b>	*	*	~			+	4	8	30	2	ខេត	3 (	Ŕ	묽	R	8	6	ì	1	e madema

## FIGURE 15(A)

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT RESULTS FOR LOT MEDPHOS (MANNITOL FORMULATION)

alysis	Peak Bi	(mg/m)	1	i		,	<b>20.02</b>	<0.02***	40,02	40.02	8.6	<0.02	1	1 4	:	<b>&lt;0.02</b>	*********	<0.02***	<0.02	<0.02	
RP-HFLC Analysis	Interferon befa-1b (Penk B+Renk B1)	(mg(m))	ţ	ŧ	1	:	0.23	0.24***	0.23***	0.23	0.24	0.25	1	1	:	0.23	0.24***	0,22***	0.22	0.23	
	Months in		٥	74	m	4	47	9	ø	72	<u>∞</u>	24	8	m	₹	w	v	σ,	12	22	
	Storage Temp.	(၁)	~	4	4	**	4	4	*	4	<b>-</b>	<b>'</b>	20	22	8	30	33	30	黑	30	

Expected Results:

\*\*\* SOP QG162 (AKA Q1052) was not followed: NLT one injection per test vial (two test vials per lot) was not performe Note: A concedion was made to the 15 month data point for RP-HPLC.

### FIGURE 15(B)

Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al.

Title: The Manage of the Stabilish of t

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT RESULTS FOR LOT MBDEN009 (MANNITOL FORMULATION)

200	1		Appearance					
Temp. Storage	Cales (es)	Upon Reconstitution	Ugan Recon. Charley	Upon Recon.	Residual	pH Upon	Potency	Container Closure Integrity
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					(% by melght)		(IU/mg x 107)	
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•	į	•			•	3	3.0	ı
7 (	YN.	NA	i	1	ć			
m + ·	white	clear, colorless	1	'	<u> </u>	1	:	1
7	ž	NA	1			7.3	2.9	1
*	MA	YAY	ì	:	20	;	:	
7	asthife.	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	1	:	1	:	1	
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7	white	clear colorless		•	ŝ	7.A	3.0	t
4 13	white		, 1	ŧ	ი გ	7.4	2.5	
7		Sterring Columns	₹ .	colorless	80	7.5	, c	ſ
\$	WINC.	cless, alightly yellow	₹	284	ě	3 3	3	;
			ł	ATTA	q n	7.7	32	Pacs
30	N/A	· VIN						
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35	NYA	SCOTON STATE	;	t	9.0	7.3	5	l
		YM	1	1	90	! !	<b>!</b>	ſ
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30 05	white	clear, allebely wellow	i	i	1		:	ı
30	white	descolvation	•	;	2	7.4	2.4	1
8	white	of section and section	1	•	a7.	7.5	C 2	i ,
	1	Charles of the Control of the Contro	1	ſ	2.0	7.6		•
	2010	clear, colorless	Ħ	colorlas	\$ .	\$	<u>.</u>	ı
	white	clear, slightly yellow	Ī		3;	7.	3.1	ſ
				70 X3	3	7.4	3.3	Pass
European Specification	White	2000	The state of the s					
		colorless to light yellow	NAT REFUI	Colodess to	NMT3%	7.1-7.8	2.21045×10 <sup>7</sup>	Pics
				NAT.BY,				

### FIGURE 16(A)

Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al Inventor(s): Wolfe et al Application Nor North Signed 12 12 12 Atty Dkt No: PP16166.003(35784/240745)

## STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT RESULTS FOR LOT MEDPNO® (MEANNITOL FORMULATION)

Storиge Тепр.	Months in	interferon beha-Ib (Reak B + Peak B1)	PeakBi
(3.)	9	(mg/m)	(lan/gar)
	0	ŧ	1
*	r		
	• •	1	ı
₹ 1		1	:
4	4	í	:
4	40	0.24	<0.02
4	ø	0.25***	<0.02***
4	Φ	0.24**	<0 US
₹	ជ	0.23	500
4	∞	0.25	2 8
₹	77	0.25	<b>€005</b>
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æ	vo	******	70.00
8	·	44870	**************************************
<b>.</b>	, <u>c</u>		<b>2000</b>
2	1 :	0.43	8,62
<b>₹</b> ∶	×	0.24	<b>₹0.0</b> ×
8	75	0.24	<b>&lt;0.02</b>
cted Result	3	Expected Resulter	200
		47.0 X C 7.0	NATORS

## FIGURE 16(B)

Inventor(s): Wolfe et al Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)

### REDUCING ACTIVITY IN MANNITOL SAMPLES

Sample	Sample	Reducing Activity	Mean Value
No.		Content (ppm)	(ppm)
1	Sample # 1 Unpurified	53.7	
2	Sample # 2 Unpurified	44.1	44.1
3	Sample # 3 Unpurified	34.4	
4	Sample # 1 Methanol Treated	19.3	
5	Sample # 2 Methanol Treated	19,2	18.5
6	Sample # 3 Methanol Treated	17.0	
7	Highly Purified Mannitol # 1	10.5	
8	Highly Purified Mannitol # 2	11.2	10.2
9	Highly Purified Mannitol # 3	8.9	